DETAILED ACTION

Applicant's amendment filed 1/29/2010 has been received and entered into the present application.

Applicant's arguments filed 1/29/2010 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 89-98 rejected under 35 U.S.C. 103(a) as being unpatentable over Benoit et al. (U.S. 6,624,154) and Reid (Current Opinion in Investigational Drugs, provided by Applicant) and Sacchi et al. (Hematological 1997; 82: 106-121), in light of Zhao (Journal of Pharmacology and Experimental Therapeutics, 2003, vol. 205, no. 2 pages 565-572) and in light of Remington's Pharmaceutical Science (pages 420-425, 1980).

Benoit et al teach the treatment of leukemia with the administration of rolipram (see claims 1, 4 and 13).

Zhao et al teach that rolipram is in fact a phosphodiesterase 4 inhibitor (see title).

Benoit et al. does not teach the use of roflumilast as the PDE type 4 inhibitor, nor does it teach the use of all trans retinoic acid as a differentiation inducing agent.

Reid teaches that roflumilast is a nonselective PDE4 inhibitor which appears to be the major PDE isoenzyme involved in the regulation of cAMP-mediated functions in airway inflammatory and structural cells (introduction). Roflumilast is substantially more potent than rolipram (page 1165, synthesis and SAR, last 3 lines) and inhibit the functions of both immunocompetent and inflammatory cells to a greater level than rolipram (page 1168, second column, last paragraph).

Redi does not teach the use of roflumilast for the treatment of myeloid leukemia, not does it teach all trans retinoic acid as the differentiation inducing agent.

Sacchi et al teach that there is considerable evidence that retinoids have a potent antiproliferative effect, and may be effective in the treatment of a variety of human diseases including cancer (page 107, column 1, first 4 lines), further ATRA (all trans retinoic acid) has proven active against a range of malignancies in isolated tissue culture systems and in human clinical trials (page 109, column 1, under Metabolism). The therapeutic use of ATRA in acute promyelocytic leukemia (APL) was pioneered in the late eighties with results of 94 percent complete remissions (CR) using ATRA alone, generating tremendous interest in the clinical use of ATRA in APL (page 111, column 2, paragraph 3). Retinoids seem to have a preferential effect on patients with mature T-cell lymphoma. L-ATRA renders B-cell lymphoma lines more susceptible to apoptosis by down-regulating bcl-2 gene expression suggesting that L-ATRA might be also useful for treating B-cell non-Hodgkin's lymphoma (page 115, column 1, first paragraph). In vitro ATRA can inhibit proliferation of myeloma cells by the downregulation of IL-6 receptors and/or its signal transducer glycoprotein 130 (gp130) surface expression on neoplastic cells, and

by inhibition of IL-6 production by myelomatous and stromal cells (page 115, column 1, under ATRA in multiple myeloma). Expanding the spectrum of hematological malignancies, that may respond to ATRA remains a challenge, but several results show some activity of retinoids alone or in combination with other drugs in juvenile chronic myelogenous leukemia, myelodysplastic syndrome, cutaneous T-cell lymphoma and chronic myelogenous leukemia. Studies exploring the potential clinical synergim of ATRA-based combination therapies (e.g., with growth factors, other differentiating agents such as vitamin D3, immunomodulators like interferons or chemotherapeutic agents appear to be especially interesting (page 116, last paragraph).

The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because Benoit et al. broadly teaches the use of a PDE 4 inhibitor, rolipram, for the treatment of a lymphoid malignancy. Although, roflumilast is not specifically disclosed by the reference, Reid teaches that that roflumilast is a PDE 4 inhibitor, which as described is more potent that rolipram. Further, Sacchi teaches the treatment of ATRA for various lymphoid malignancies.

Considering the teachings of Benoit et al. who discloses the use of a PDE4 inhibitor for the treatment of a lymphoid malignancy, and also considering that it is well known in the art that roflumilast is a PDE4 inhibitor, but also that it is more potent than roflumilast and that additionally ATRA is used for the treatment of various lymphoid malignancies, it would have been obvious to one of ordinary skill in the art to use roflumilast as the PDE4 inhibitor for the treatment of myeloid leukemia. Such a person would have been motivated to employ such roflumilast with a reasonable expectation to provide the same or similar therapeutic effects as rolipram disclosed by Reid and, further, because it is more potent than rolipram.

Further, one would have been motivated to additionally administer ATRA since it is also well known for the treatment of lymphoid malignancies. One of ordinary skill in the art would have been motivated to combine the teachings above since as combined would teach the invention as claimed. The idea of combining the administration of an agent known to be useful in the treatment of lymphoid malignancies flows logically from having been taught in the prior art.

The use of pharmaceutically acceptable salts of the elected compound would have been a matter well within the purview of the skilled artisan. As taught by Remington's Pharmaceutical Sciences, drugs may be formulated into salts to modify the duration of action of a drug; to modify the transportation and distribution of the drug in the body; to reduce toxicity; and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself (see column 2 of page 424, first paragraph). Thus, it would have been obvious to the skilled artisan motivated by any one or more of these factors to formulate the active agent into a pharmaceutically acceptable salt to enhance the pharmacokinetic parameters of the drug or to reduce the toxicity with the reasonable expectation that the therapeutic benefit of the agent in salt form would have been the same or substantially similar to that of the agent itself.

Response to Applicant's Remarks

The entirety of Applicant's response seems to be drawn to the newly amended claim which states "a combination of active compounds, which ***consists*** *of a first active compound and a second active compound." Given this amendment Applicant contends that the cited art of Benoit et al., Reid, Sacchi et al. and Zhao et al. has been overcome.* This is not found persuasive. Applicant's attention is drawn to the breadth of their own claim. Claim 89 states "a method for treating acute myeloid leukemia (AML) in a mammal, comprising administering to said mammal a therapeutically effective amount…" Applicant's attention is therefore drawn to both the open and closed language recited in independent claim 89. Given

the current amended claim, the claims are interpreted as having open language. Therefore, the prior art reads on the instant claim.

Conclusion

No claim is found to be allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642